REMARKS/ARGUMENTS

I.   Rejections Under 35 USC § 112

Examiner rejected Claims 1, 13-17, 29-31, and 46 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Specifically, Examiner stated that the specification does not provide support for the specific limitation of "dipeptidyl peptidase-IV inhibitors" but only for the more generic "dipeptidyl peptidase inhibitors."

Applicant submits the specification provides support for both dipeptidyl peptidase inhibitors and dipeptidyl peptidase-IV inhibitors. Paragraph 28 of the specification incorporates by reference U.S. Patent No. 6,110,949 to Villhauer and further states that Villhauer discloses useful dipeptidyl peptidase inhibitors for use in the present invention. Villhauer describes many dipeptidyl-peptidase-IV inhibitors, the disclosure of which should be treated as if it were part of the text of the application as filed. See MPEP § 2163.07(b) ("The information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed.")   "The function of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him." In re Edwards, 196 U.S.P.Q. 465, 467 (CCPA 1978). Because Villhauer discloses and describes dipeptidyl peptidase-IV inhibitors and because Villhauer was properly incorporated by reference in the present application at the time of filing, the written description requirement has been met. Accordingly, Applicant respectfully requests that the 35 U.S.C. § 112, first paragraph, rejection be withdrawn.

II.   Rejection Under 35 USC § 103

Examiner rejected Claims 1, 13-17, 29-31, and 46 under 35 USC § 103(a) as being unpatentable over WO 1997/041097 to Lohray *et al.* in view of U.S. Patent No. 6,011,155 to Villhauer. Specifically, the Examiner stated that Lohray *et al.* teaches a composition comprising balaglitazone that is useful in treating type II diabetes and insulin resistance associated with obesity and Villhauer teaches a pharmaceutical composition comprising a dipeptidyl peptidase-IV inhibitor that is useful in treating mammals with noninsulin dependent diabetes mellitus and obesity. The Examiner further stated that it would be prima facie obvious to combine the two references based on their similar uses.

It is improper, in determining whether a person of ordinary skill would have been led to this combination of references, simply to "[use] that which the inventor taught against its teacher." *In re Lee,* 277 F.3d 1343, 1338, 61 U.S.P.Q.2d 1430 (Fed. Cir. 2002). In the present case, neither Villhauer or Lohray provide any indication that balaglitazone and dipeptidyl peptidase-IV inhibitors should be combined for any purpose. There is simply no suggestion in either reference for combining the two compositions. Instead, the Examiner has improperly used the present specification as a blueprint to reconstruct the claimed invention and has failed to establish a *prima facie* case of obviousness.

In addition, Applicants have provided a declaration illustrating the unexpected synergistic results of the present invention. More particularly, the declaration is based on test results of the combination of balaglitazone and a dipeptidyl peptidase-IV inhibitor, Vildagliptin. As seen from the tests results, the combination of the two

compounds provides a synergistic effect. The effect is greater than the expected combined results of the two compounds individually. Specifically, as stated in the declaration and accompanying tests results, the combination of balaglitazone and a dipeptidyl peptidase-IV inhibitor had synergistic results with respect to the reduction of plasma lipids, both TG and FFA above and beyond what was predicted from the use of either compound in mono-therapy. Accordingly, the increased benefits exemplified by the combination of the two compounds create a novel invention which would not be obvious to one skilled in the art.

In view of the foregoing arguments, Applicants respectfully submit that the rejected claims are patentably distinct over the references cited by the Examiner and meet all other statutory requirements. We believe that the present Application is now in complete condition for allowance and, therefore, respectfully request the Examiner to reconsider the rejections in the Office Action and allow this Application.
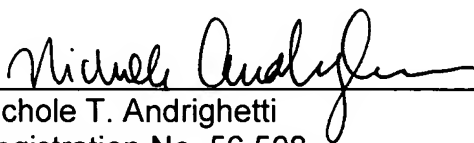
We invite the Examiner to telephone the undersigned should any issues remain after the consideration of this response. Please charge any additional fees that may be required to Deposit Account No. 50-2548.

Respectfully requested,

NELSON MULLINS RILEY & SCARBOROUGH

December 30, 2008
Date

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Summary

SHORT SUMMARY

Zucker Diabetic Fatty (ZDF) rats received oral administration of either vehicle BID, balaglitazone 5 mg/kg QD, LAF-237 3 mg/kg BID or the combination of balaglitazone 5 mg/kg QD and LAF-237 3 mg/kg BID for 42 days. Treatment with LAF-237 did not change body weight or the size of fat depots, increased plasma GLP-1 (fasting and during OGTT), decreased fasting plasma glucose and reduced HbA1c, although not to the same extent as balaglitazone or balaglitazone combined with LAF-237. Treatment with balaglitazone either alone or in combination with LAF-237 increased body weight and fat depot sizes, increased insulin secretion and reduced HbA1c (to the same extent as balaglitazone alone). In addition, Balaglitazone combined with LAF-237 increased plasma GLP-1 (fasting and during OGTT), and synergistically reduced plasma lipids (TG and FFA) above and beyond what could be predicted from use of either compound in mono-therapy.

The robust HbA1c lowering effect of balaglitazone makes it a promising candidate for treatment of type-2 diabetes. Furthermore, the combination of balaglitazone with a DDP-IV inhibitor may be a promising treatment regimen for type-2 diabetes patients suffering from dyslipidaemia.

TITLE OF STUDY

Efficacy of balaglitazone and LAF-237 combination therapy on glycaemic control in severely diabetic rats.

INTRODUCTION

Both alone and in combination with conventional anti-hyperglycaemic agents (metformin, sulfonylureas), GLP-1 therapy has been shown to improve glycaemic control in severely advanced clinical cases of human type 2 diabetes (Kendall et al., 2004). However, it is likely that certain MODY patients as well as grossly obese type 2 diabetes patients become in need of more efficacious combination therapy than tested so far. Possible therapeutic strategy would include combination of GLP-1 agents with peripherally acting insulin sensitizers such as PPARγ agonists. To further investigate the potential additive therapeutic effects on glycaemic control variables, a combination study of balaglitazone and LAF-237 has been designed.

RESULTS and CONCLUSIONS

Six weeks of treatment with balaglitazone
- increased body weight and fat depot size
- increased insulin secretion
- reduced HbA1c (significantly more than LAF-237 mono-therapy)

Six weeks of treatment with LAF-237
- did not change body weight and size of fat depots
- decreased fasting plasma glucose
- reduced HbA1c but not to the same extend as balaglitazone
- increased plasma GLP-1 (fasting and during OGTT)

Six weeks of treatment with balaglitazone combined with LAF-237
- increased body weight and fat depot size
- increased fasting plasma insulin
- increased plasma GLP-1 (fasting and during OGTT)
- reduced HbA1c (similar to balaglitazone mono-therapy)
- reduced fasting plasma TG level
- reduced fasting plasma FFA level

Balaglitazone shows an HbA1c lowering effect that is very robust and promising for future treatment of type-2 diabetes.

In addition, the combination of balaglitazone and a DPP-IV inhibitor (LAF-237) reveals a lowering effect on plasma lipids that was unpredictable based on results from mono-therapy results. Therefore, the combination of balaglitazone with a DPP-IV inhibitor may

be a very promising treatment regimen for type-2 diabetes patients suffering from dyslipidaemia.

Background

Zucker diabetic fatty (ZDF) rats are commonly used as a rodent model of type 2 diabetes (Etgen and Oldham, 2000). Compared to wild type and heterozygous controls, homozygous male ZDF rats are severely insulin resistant and have compensatory hyperinsulinaemia at young age progressing to beta cell failure at more advanced age. Chronic monotherapy of male ZDF rats with conventional and novel antihyperglycaemic compounds is incapable of normalising fasting plasma glucose levels. Thus, maximally efficacious doses of the partial PPARγ agonist balaglitazone or the DPPIV inhibitor LAF237 (vildagliptin; which increases circulating levels of GLP1) have been shown to incapable of completely restoring glycaemic control in male ZDF rats.

A major therapeutic challenge met when treating people with type 2 diabetes is the commonly associated diabetic dyslipidaemia. Thus, people with type 2 diabetes have an approximately 4 fold higher risk of suffering fatal myocardial ischemia when compared to people without diabetes. It is generally believed that the dyslipidaemia accompanying type 2 diabetes is in part contributing to the increased risk of cardiovascular hazard. It is at present unclear whether all therapeutic strategies aiming at decreasing triglycerides in people with type 2 diabetes are efficacious in lowering incidences of myocardial ischemia. However, in the FIELD study fenofibrate induced reduction of plasma triglyceride levels was without impact on hard cardiovascular end points in people with type 2 diabetes. This observation suggests that triglyceride reduction without concomitant improvement of insulin sensitivity is a futile strategy for risk reduction of macrovascular disease.

Both alone and in combination with conventional anti-hyperglycaemic agents (metformin, sulfonylureas), GLP-1 therapy has been shown to improve glycaemic control in severely advanced clinical cases of human type 2 diabetes (Kendall et al., 2004). However, it is likely that certain MODY patients as well as grossly obese type 2 diabetes patients become in need of more efficacious combination therapy than tested so far. Possible therapeutic strategy would include combination of GLP-1 agents with peripherally acting insulin sensitizers such as PPAR-γ agonists. Rheoscience A/S and Dr. Reddy are jointly developing a partial PPAR-γ agonist, balaglitazone, which is currently in clinical development. To further investigate the potential additive therapeutic effects on glycaemic control variables and plasma surrogate markers of cardiovascular risk, a combination study of balaglitazone and LAF-237 was carried out.

1 Aim of the study

1.1 Primary objective

a) To assess potential additive anti-hyperglycaemic efficacy of combining balaglitazone with LAF-237.

b) To assess potential additive pancreas protective effect of combining balaglitazone with LAF-237.

1.2 Secondary objectives

a) To assess effects of sub-chronic treatment with balaglitazone and LAF-237 either alone or in combination on food intake, body weight and body composition.

b) To assess effects of sub-chronic treatment with balaglitazone and LAF-237 either alone or in combination on plasma lipid profile

2 Experimental protocol

2.1 Animals

Fifty-four (54) male Zucker diabetic fatty (ZDF) rats were obtained from Charles River, Belgium. Animals were scheduled to arrive at Rheoscience animal research facilities at 11-12 weeks of age. Upon arrival to the animal unit, rats were housed with one rat per cage and allowed to acclimatise for two weeks. Rats were housed under a normal light cycle (light from 0600-1800 h) at controlled temperature conditions with ad libitum access to chow (Purina 5008) and water. **Measurements of 24 hour food and water intake** were carried out weekly on days 0, 1, 8, 15, 22, 29, 36, and 41 (final measurement of food intake on the numbered day, i.e. food intake on day 0 was between day −1 and day 0).

All animal experiments were conducted in accordance with Rheoscience bio-ethical guidelines, which are fully compliant to internationally accepted principles for the care and use of laboratory animals. The described experiments were covered by personal licenses to Philip J. Larsen (2004/561-859) issued by the Danish Committee for Animal Research.

The study was preceded by three days of mock dosing. Three days before initiation of dosing, rats were stratified into 4 groups (n=11) according to HbA1c (i.e. 10 animals are discarded):

Group 1: Vehicle BID + vehicle QD (n=11)

Group 2: Balaglitazone, 5 mg/kg QD + Vehicle BID (n=11)

Group 3:   LAF-237, 3 mg/kg BID + vehicle QD (n=11)

Group 4:   Balaglitazone, 5 mg/kg QD + LAF-237, 3 mg/kg BID (n=11)

2.2   Compounds and dosing

Vehicle: 10% Hydroxypropyl beta-Cyclodextrin (w/v)

All animals were dosed twice daily (between 7:00 and 8:00 and between 15:00 and 16:00).

Compound and/or vehicle were administered twice daily as oral gavage (1.2 ml/kg (corresponding to approximately 500 µl/dose)).

2.3   Basal metabolic parameters

Twenty four hours food intake and body weight was measured weekly (from 7:00 AM to 8:00 AM). On day -3 and 42 a blood sample for HbA_{1c} measurement was taken.

2.4   Oral Glucose Tolerance Test (OGTT)

This test was carried out at 8:00 AM on the day before termination of the experiment (day 42). Animals were mildly fasted as they had had access to only 50% of their daily energy requirements in the preceding 20hrs (Since 12:00 AM the previous day). Blood samples were taken from a tail vein. Plasma glucose was measured at time points: -30, 0, 15, 30, 60, 90, 120, and 180 minutes after oral administration of 2g/kg glucose (Glucose 500mg/ml, Fresenius Kabi, Sweden). The oral glucose load was given as gavage via a gastric tube connected to a syringe ensuring accurate dosing. P-insulin and GLP-1 was measured at time points: 0, 15, 30, 60, 90, 120, and 180 minutes using a Rat Endocrine Immunoassay Panel (Lincoplex, analyzed using a Luminex100TM system (Linco Research, USA)). A baseline blood sample of 500 µl was taken at time t=-30 min from the tail vein. A sample of this size allowed for analysis of both glycaemic and lipid variables (see below).

2.5   Blood sampling and plasma measurements

All plasma samples were labelled with the following data:

Protocol Number
Date of sampling
Time of sampling.
Animal Number

5

Type of sample

Plasma-Glucose, Plasma-total Cholesterol, Plasma-triacylglycerol was measured using standard enzyme assay kits on a fully automated analyser (Vitros DTII). Plasma non-esterified free fatty acids (NEFA) were determined by a spectrophotometer using acyl-CoA oxidase based colorimetric kit (NEFA-C, WAKO pure chemicals, Osaka, Japan). Samples taken in serum Vacutainer+1%NaF are used for FFA analyses. HbA1c was measured using a filter photometer (DCA2000, Bayer Health Care).

Plasma insulin and GLP-1 were measured using a Rat Endocrine Immuno-assay Panel (Lincoplex, analyzed using a Luminex100TM system (Linco Research, USA)). Assays were performed as recommended by the manufacturers with the exception that the GLP-1 fluorescence data were corrected (25 counts subtracted from each standard value) because the background levels were lower when measuring plasma from Zucker diabetic fatty rats than in standard samples supplemented with the serum matrix supplied with the kit.

Terminal blood samples (minimum 600 µl plasma) were collected in heparinised/LiCl containing tubes and kept on ice for a minimal amount of time (no more than 30 minutes) until they were centrifuged at 2800 x G for 10 minutes at 4 °C. Plasma obtained from these samples was kept frozen at -80 °C. Frozen plasma obtained from terminal blood samples was stored for exposure analysis.

2.6 Body composition and termination

The day after the OGTT, animals were trunk bled and bulk of this sample was kept for exposure studies. Body white adipose tissue compartments were removed from exsanguinated rats and weighed. Fat depot analysis included retroperitoneal, epididymal and subcutaneous inguinal fat. The Pancreas was removed by dissection the entire mesenterial adipose tissue block, which was transferred to 4 % paraformaldehyde (section 2.10).

2.7 Data, reporting, and Statistical Evaluation

All data were collected and fed into sheets designed and provided by Rheo-science

All data are presented graphically using Graph Pad Prism. Statview software is used for the statistical analysis. Data are analysed using one-way analysis of variance (ANOVA). Results are presented as mean±SEM (standard error of the mean) unless otherwise stated. Statistical evaluation of the data was carried out using one-way analysis of variance (ANOVA) with Fishers post-hoc analysis between control and treatment groups in cases where statistical significance was established ($p<0.05$).

3 Results

3.1 General observations

No observations of abnormal behaviour (e.g. alertness, aggressive behaviour, excessive grooming) were recorded by acute or chronic (42 days) treatment with balaglitazone or LAF-237.

3.2 Body weight, food- and water intake

Body weights were recorded once weekly. The obtained data were expressed both as actual body weight (gram) and body weight gain in percent of the average body weight of day 0.

In vehicle treated ZDF rats, body weight stagnated.

Treatment with balaglitazone 5 mg/kg QD either alone or in combination with LAF-237 resulted in increased body weight and percent body weight gain compared to vehicle treated animals from day 7 and throughout the study (Fig. 2-3 and Table 1). Treatment with LAF-237 alone had no effect on body weight or percent body weight gain.

Twenty-four hours food intake was recorded once weekly together with water intake. Treatment with balaglitazone 5 mg/kg QD resulted in increased food intake day 8 and balaglitazone given in combination with LAF-237 resulted in increased food intake day 15 and 22 compared to vehicle treated animals (Fig. 4; table 2). LAF-237 treatment resulted in decreased food intake day 8 and 29 compared to vehicle treated animals. The general pattern for the whole dosing period is that balaglitazone 5 mg/kg QD either alone or in combination with LAF-237 resulted in a general increased food intake whereas LAF-237 alone lowered food intake.

Twenty-four hours water intake was decreased day 1, 8 and 15 in LAF-237 treated animals and day 8 in balaglitazone and balaglitazone+LAF-237 treated animals (Fig. 5 and Table 2).

3.3 Oral glucose tolerance test

On the last dosing day (day 42), rats were subjected to an oral glucose tolerance test (OGTT) in the semi-starved state. When calculating the area under the curve (AUC) obtained from the resulting plasma glucose concentration profile (area above 0 mmol/l plasma glucose), animals treated with LAF-237 tended to have a lower AUC compared to vehicle (p=0.065; Fig. 6 and Table 3).

Insulin release during the OGTT was also measured. Areas under the curve of the resulting insulin secretion profiles were calculated and compared between groups (Fig. 7, table 3). Treatment with balaglitazone showed significantly elevated integrated insulin secretion compared to vehicle treated animals (p<0.05). Treatment with balaglitazone in combination with LAF-237

(p=0.06) and treatment with LAF-237 (p=0.075) tended to elevate integrated insulin secretion compared to vehicle treated animals.

GLP-1 release during the OGTT was also measured. Areas under the curve of the resulting GLP-1 secretion profiles were calculated and compared between groups (Fig. 8, table 3). Treatment with LAF-237 either alone or in combination with balaglitazone showed significantly elevated integrated GLP-1 secretion compared to vehicle treated animals (p<0.05 for both treatments).

3.4 HbA1c

HbA1c was measured three days prior to the initiation of the study and used as stratifying parameter for the groups. The baseline HbA1c value (day -3) was 7.8±0.2 % in all groups (Fig. 1 and Table 4).

On day 42, HbA1c was re-measured. There had been an increase of 2 % in HbA1c since day -3 as HbA1c had increased to 9.8±0.2 % in vehicle treated animals. Compared to vehicle, both balaglitazone and LAF either alone or in combination decreased HbA1c (p<0.05 for all treatments vs. vehicle; Fig. 9A and Table 4). Balaglitazone was more efficacious in lowering HbA1c than LAF-237 (p<0.05 balaglitazone vs. LAF-237) and the combination treatment of balaglitazone and LAF-237 was not more efficacious than balaglitazone alone.

These longitudinal changes form day -3 to day 42 in HbA1c are summarized in Fig. 9B, showing the 2% increase in vehicle treated animals from day -3 to day 42 (p<0.05; paired t-test). Balaglitazone treatment alone protected for this elevation in HbA1c (ns; paired t-test) whereas LAF treatment alone was not able to fully protect against HbA1c elevations (p<0.05; paired t-test). The combination of balaglitazone and LAF-237 displayed the same level of protection as balaglitazone alone (ns; paired t-test).

3.5 Blood biochemistry

On the last day of dosing (day 42 at t_{-30} relative to oral glucose challenge) fasting plasma levels of glucose, insulin, GLP-1, triacylglycerol (TG), total cholesterol and non-esterified free fatty acids (FFAs) were measured (Fig. 10-15 and Table 4).

Plasma-glucose levels were significantly lower in the groups where LAF-237 was given alone (p<0.05) or in combination with balaglitazone (p<0.05) compared to vehicle treated animals (Fig. 10 and Table 4). Balaglitazone treatment alone did not lower fasting plasma glucose. The fact that HbA1c was markedly lower proves that balaglitazone has a marked effect on plasma glucose levels. The reason behind the absence of effect on fasting blood glucose in balaglitazone treated animals (alone or additive effect in the combination with LAF-237) may be found in the fact that animals treated with balaglitazone have a much higher 24-hour food intake and thus have a relative more filled ventricle and GI-tract at the time of initiation of the OGTT.

Compared to vehicle treated animals, fasting plasma insulin concentrations were markedly increased in animals treated with balaglitazone combined with LAF-237 ($p < 0.05$ vs. vehicle; Fig. 11 and Table 4) and tended to be increased following mono-treatment with balaglitazone ($p = 0.66$) or LAF-237 ($p = 0.085$).

Animals treated with LAF-237 either alone ($p < 0.05$) or in combination with balaglitazone ($p < 0.05$) had increased levels of fasting plasma GLP-1 compared to vehicle treated animals (Fig. 12 and Table 4).

Compared to vehicle treated animals, plasma levels of TG were significantly reduced in animals treated with combined balaglitazone and LAF237 ($p < 0.05$; Fig. 13 and Table 4).

There was no difference in the level of total plasma cholesterol between any of the treatment groups and vehicle treated animals (Fig. 14 and Table 4).

Plasma concentrations of free fatty acids were reduced in animals treated with balaglitazone combined with LAF-237 ($p < 0.05$; Fig. 15 and Table 4).

3.6 Fat Depot Analysis

On the day following the OGTT, subcutaneous inguinal fat, epididymal fat, and retroperitoneal fat was isolated and weighed. All three fat depots had increased in animals treated with balaglitazone either alone ($p < 0.05$) or in combination with LAF-237 ($p < 0.05$) compared to both vehicle treated and to LAF-237 mono-treated animals (Fig. 16-18 and Table 5). LAF-237 mono-treated animals had fat depot sizes similar to vehicle treated animals.

4 Conclusion

Six weeks of treatment with balaglitazone
- increased body weight and fat depot size
- increased insulin secretion
- reduced HbA1c (more than LAF-237 mono-therapy)

Six weeks of treatment with LAF-237
- did not change body weight and size of fat depots
- decreased fasting plasma glucose
- reduced HbA1c but not to the same extend as balaglitazone
- increased plasma GLP-1(fasting and during OGTT)

Six weeks of treatment with balaglitazone combined with LAF-237
- increased body weight and fat depot size
- increased fasting plasma insulin
- increased plasma GLP-1 (fasting and during OGTT)
- reduced HbA1c (similar to balaglitazone mono-therapy)

- reduced fasting plasma TG level
- reduced fasting plasma FFA level

Balaglitazone shows an HbA1c lowering effect that is very robust and promising for future treatment of type-2 diabetes.

In addition, the combination of balaglitazone and a DPP-IV inhibitor (LAF-237) reveals a lowering effect on plasma lipids that was unpredictable based on mono-therapy results. Therefore, the combination of balaglitazone with a DPP-IV inhibitor may be a very promising treatment regimen for type-2 diabetes patients suffering from dyslipidaemia.

5 Appendix

5.1 Figures

PowerPoint file: RHS2006-089-RHS Figures-Final

5.2 Tables

Table 1: Body weight and body weight gain compared to vehicle treatment (n=11)

	Vehicle	Balaglitazone 5mg/kg	LAF-237 mg/kg	Bala+LAF-237
Body weight (g), day 7	393.2±5.0	414.7±5.1*	393.2±3.7	414.7±6.4*
Body weight (g), day 14	391.2±4.9	433.8±5.6*	392.5±3.2	433.0±6.7*
Body weight (g), day 21	402.9±4.9	461.8±6.2*	403.2±4.2	452.5±8.0*
Body weight (g), day 28	402.0±4.8	474.6±6.6*	400.6±4.6	466.4±8.8*
Body weight (g), day 35	416.1±3.9	489.9±7.7*	407.9±4.4	481.1±9.4*
Body weight (g), day 41	409.9±7.5	499.9±8.8*	413.2±4.3	489.4±9.5*
BW gain (%), day 7	102.1±0.5	107.7±0.5*	101.7±0.6	106.2±0.6*
BW gain (%), day 14	102.1±0.7	112.7±0.9*	101.5±0.7	111.5±0.8*
BW gain (%), day 21	104.7±1.3	119.9±1.2*	104.3±0.9	116.5±1.0*
BW gain (%), day 28	104.4±1.0	123.3±1.2*	103.6±1.2	120.1±1.1*
BW gain (%), day 35	108.1±0.6	127.2±1.3*	105.5±1.0	123.8±1.3*
BW gain (%), day 41	106.5±1.8	129.8±1.4*	106.8±1.0	126.0±1.2*

* $p < 0.05$ vs. vehicle, ANOVA followed by Fisher PLSD

Table 2: Food intake and water intake compared to vehicle (n=11 unless otherwise stated)

	Vehicle	Balaglitazone 5mg/kg	LAF-237 mg/kg	Bala+LAF-237
Food intake (g/day), day 1	46.0±1.1	45.6±1.1	42.8±1.2, $^{p=0.058}$	46.2±1.1
Food intake (g/day), day 8	45.5±1.0	50.2±1.2*	39.0±1.1*	48.2±1.3
Food intake (g/day), day 15	46.2±1.3	50.8±1.7, $^{p=0.062}$	41.4±1.9, $^{p=0.051}$	52.0±1.8*
Food intake (g/day), day 22	49.6±1.3 n=4	52.4±2.2, $^{p=0.058}$ n=6	44.6±1.6, $^{p=0.075}$ n=5	54.7±1.3* n=6
Food intake (g/day), day 29	48.6±1.8	52.7±1.8	40.6±2.5*	51.6±1.4
Food intake (g/day), day 36	47.2±1.6	51.0±1.7	44.6±1.3	50.6±1.4
Food intake (g/day), day 41	43.1±5.2 n=5	47.6±2.1 n=6	47.6±0.6 n=5	50.2±1.3 n=6
Water intake (g/day), day 1	171.2±8.5	162.1±4.9	147.0±7.8*	154.0±6.3
Water intake (g/day), day 8	182.6±9.3	160.2±6.2*	152.2±5.4*	156.8±8.3*
Water intake (g/day), day 15	181.0±7.5	162.4±8.1	147.1±9.0*	160.6±12.4
Water intake (g/day), day 22	175.0±15.8	193.1±6.8	165.9±8.3 n=10	180.7±8.4
Water intake (g/day), day 29	201.4±16.6 n=5	198.5±9.6 n=6	171.9±13.5 n=5	194.7±9.0 n=6
Water intake (g/day), day 36	194.0±14.9 n=5	188.6±8.7 n=4	176.8±4.9 n=4	182.4±7.4 n=6
Water intake (g/day), day 41	173.4±27.2 n=5	190.4±7.5 n=6	192.9±3.0 n=5	199.5±12.1 n=6

* $p < 0.05$ vs. vehicle, ANOVA followed by Fisher PLSD

Table 3: Oral glucose tolerance test (day 42)

	Vehicle	Balaglitazone 5mg/kg	LAF-237 mg/kg	Bala+LAF-237
AUC glucose (mM*min)	7175±63 n=8	7078±217 n=9	6724±96, $p=0.065$ n=9	6911±191 n=10
AUC insulin (pM*min) x10^3	36.1±1.8 n=11	44.5±2.9* n=10	43.1±2.7, $p=0.075$ n=10	43.3±3.2, $p=0.060$ n=11
AUC GLP-1 (pM*min)	3173±387 n=7	2654±634 n=4	7700±454* n=11	7143±596* n=11

* $p<0.05$ vs. vehicle, ANOVA followed by Fisher PLSD

Table 4: HbA1c (day -3 and 42), fasting plasma glucose, insulin, GLP-1, TG, total cholesterol, FFA (day 42) (n=11 unless otherwise stated)

	Vehicle	Balaglitazone 5mg/kg	LAF-237 mg/kg	Bala+LAF-237
HbA1c (%), day -3	7.8±0.2	7.8±0.2	7.8±0.2	7.8±0.2
HbA1c (%), day 42	9.8±0.2	8.1±0.1*¶	8.9±0.2*	8.0±0.2*¶
Glucose (mM)	30.0±0.9	29.1±0.8	27.4±0.6*	27.6±1.0*
Insulin (pM)	197.5±12.2	258.0±20.5, $p=0.066$ n=10	252.7±28.7, $p=0.085$	262.9±24.3*
GLP-1 (pM)	18.8±1.4 n=8	13.9±2.1 n=10	46.7±5.2*	44.8±4.9*
TG (mM)	5.0±0.4	4.9±0.2	4.7±0.4	3.4±0.3*
Cholesterol (mM)	7.2±0.2	7.8±0.2	8.0±0.6	7.5±0.3
FFA (mEq/L)	0.67±0.03	0.62±0.06 n=10	0.60±0.03 n=10	0.52±0.05*

* $p<0.05$ vs. vehicle, ANOVA followed by Fisher PLSD

¶ $p<0.05$ vs. LAF-237, ANOVA followed by Fisher PLSD

Table 5: Fat depots and organ weight (day 28) (n=11)

	Vehicle	Balaglitazone 5mg/kg	LAF-237 mg/kg	Bala+LAF-237
Subcutaneous inguinal fat (g)	9.4±0.5	16.4±0.7*¶	10.1±0.6	16.0±0.5*¶
Epididymal fat (g)	7.7±0.3	10.2±1.0*¶	7.8±0.2	10.8±0.4*¶
Retroperitoneal fat (g)	14.2±0.5	24.0±0.9*¶	14.8±0.5	22.1±0.8*¶

* p<0.05 vs. vehicle, ANOVA followed by Fisher PLSD

¶ p<0.05 vs. LAF-237, ANOVA followed by Fisher PLSD